CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202834Orig1s000

OFFICE DIRECTOR MEMO

Deputy Office Director Decisional Memo

Date	(electronic stamp)
From	Robert Temple, MD
Subject	Deputy Office Director Decisional Memo
NDA/BLA # **Supplement #**	202834
Applicant Name	Eisai Inc.
Date of Submission	12/22/2011
PDUFA Goal Date	10/22/2012
Proprietary Name / **Established (USAN) Name**	FYCOMPA (perampanel) Tablets
Dosage Forms / Strength	Immediate Release Tablet (2, 4, 6, 8, 10 and 12 mg)
Proposed Indication(s)	1. Adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalized seizures in patients with epilepsy aged 12 years and older
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Martin Rusinowitz, Mary Doi, Sally Yasuda
Statistical Review	Kun Jin, Ququyan Liu
Pharmacology Toxicology Review	Lois Freed, Christopher Toscano
CMC Review/OBP Review	Martha Heimman, Lyudmila Soldatova, Tien-Mien Chen
Microbiology Review	
Clinical Pharmacology Review	Xinning Yang, Joo-Yeon Lee
OPDP	
OSI	
CDTL Review	Norman Hershkowitz
OSE/DEpi	
OSE/DMEPA	Loretta Holmes, Irene Z. Chan
OSE/DRISK	Kendra Worthy, Mary Demspey
Other – Div Dir Review Dep Dir for Safety Review	Russell Katz

OND=Office of New Drugs
OPDP=Office of Prescription Drug Products
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPi= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

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I. Introduction

Perampanel is a non-competitive selective antagonist of the AMPA (alpha-amino-3-hydroxy-5-methly-4-isoxazoleprapionic acid) receptor, a receptor that mediates cortical glutamatergic transmission. The major clinical trials (3), studies 304, 305, 306, were all placebo-controlled dose-response studies of similar design in patients with refractory (to 1 to 3 drugs) partial seizures (at least 5 seizures during the 6 week pre-randomization period, and at least 2 in each 3 week period). Perampanel was titrated weekly by 2 mg/day increases from 2-12 mg over six weeks, after which dose was to be maintained for a 13-week maintenance period. The initial analysis was to be based on the maintenance period (13 weeks), called ITT analysis by the sponsor, but FDA urged use of the full 19 week period (full ITT also called in ITT in Dr. Katz's review). This is discussed in Dr. Liu's review and she concludes study 304 is not really positive because although full ITT was successful at the 8 mg dose, ITT (the planned analysis) and the full ITT was used after results were known and for some reason (actually for reasons incomprehensible to me) the sponsor used an analytic plan that analyzed 8 mg first, and considered 12 mg only if 8 mg was < 0.05. In the study 004 ITT (the planned analysis) was nominally significant at $p < 0.05$ only for the 12 mg dose, so the 8 mg results, which needed to be positive to reach the 12 mg dose analysis, was negative and the study thus was negative.

Given the 3 similar studies, this may not matter much. I am somewhat doubtful about the full ITT because it includes several weeks (out of 19) where blood levels of perampanel would be very low. But given our preference for full ITT we probably would have insisted on this analysis anyway. As Dr. Liu's review of 8/30/2012 shows, in her tables 14-16, the median effect sizes and differences from placebo are very similar with both analyses and the full ITT effect size is not smaller, as one might have expected. In any case, the 3 studies provide clear evidence that perampanel reduces seizure frequency, as measured by median effect or an important secondary endpoint, patients with a 50% reduction in seizure rate (the placebo-subtracted rates are my rough calculation). Results are shown in Table 1. In this memo I have not re-discussed matters already considered fully by Drs. Katz and Hershkowitz.

II. Discussion of Effectiveness

A. Effect Size

Although it is recognized that the patients in the 3 trials are relatively refractory, the effects of perampanel are fairly modest, about a 20% greater than placebo reduction in median seizure rate in the best group in each of the 3 studies; a change of about 2-2.5 seizures per 28 days on average. It is also true, however, that in studies 305 and 306, effective doses (8-12 mg) reduced seizures by > 50% in almost 20% more patients than did placebo. Indeed, in the figure in labeling showing reduction in seizure frequency (fig 1) for pooled data, about 12% of patients on treatment had reductions of over 60%.

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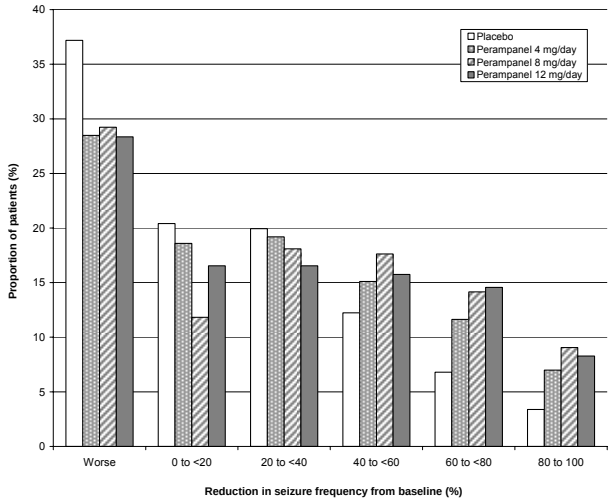
Table 1 – Full ITT analyses

Study 304				
	Placebo	4 mg	8 mg	12 mg
n	121	------	133	133
Pre-Rx seizure rate	13.7	------	14.3	12.0
Median % change	-2.1	------	-26	-34
Placebo-subtracted %	---	------	13.5	-20.1
p-value	---	------	0.0261	0.0158
50% responder %	26.4	------	37.6	36.1
Placebo-subtracted %	------	------	10.22.2012	9.7
p-value	------	------	0.076	0.091
Study 305				
n	136	------	129	121
Pre-Rx seizure rate	11.8	------	13.0	13.7
Median % change	-9.7	------	-30.5	-17.6
Placebo-subtracted %	------	------	-19.0	-13.7
p-value	------	------	0.0008	0.0105
50% responder %	14.7	------	33.3	33.9
Placebo-subtracted %	------	------	18.6	19.2
p-value	------	------	0.0018	0.0006
Study 306				
n	184	172	169	------
Pre-Rx seizure rate	9.3	10.0	10.9	------
Median % change	-10.7	-23.3	-30.8	------
Placebo-subtracted %	------	-13.7	-20.1	------
p-value	------	0.0026	< 0.0001	------
50% responder %	17.9	28.5	34.9	------
Placebo-subtracted %		10.6	17.0	------
p-value		0.132	0.0003	------

Fig 1



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Given the relatively low baseline seizure rate (10-15 per 28 days, we examined whether the 50% responder rates were similar in patients above and below the median baseline frequency. An analysis by Dr. Liu showed that in studies 305 and 306, where perampanel had its largest effects, the effect size was somewhat smaller in patients above the median seizure rate.

B. Use of CYP450 inducing drugs

The studies in Table 1 do not clearly show an improved response for 12 mg vs 8 mg (although 8 mg seems superior to 4 mg) and we were initially inclined to recommend only doses up to 8 mg (given the dose-related toxicity (see section III). This issue is complicated by use in over 50% of patients of cytochrome P450 inducers (carbamazepine, oxcarbazepine, or phenytoin), which decrease perampanel blood levels by 50-67%, obviously a problem given the fairly steep dose-response relationship between 4 and 8 mg (i.e., being on an inducer reduces blood levels of a patient on 8-12 mg to a level that would be seen with 4 mg). As a table in (b) (4) (Table 2) for pooled data from studies 304, 305, 306:

Table 2
Median % reduction in seizure rate (placebo-subtracted)

	Without Inducers	With Inducers
4 mg	15.3%	11.9%
8 mg	25.7%	14.4%
12 mg	33.2%	19.2%

(b) (4), but in data extracted from MOR, Tables 27, 28 a similar finding is present for 50% seizure reduction rate in studies 304, 305 pooled.

Table 3
Rate of 50% Reduction

304-305	Without Inducers	With Inducers
8 mg	35%	11-17%
12 mg	39%	13-18%
306		
4 mg	5.4	9%
8 mg	20.2	16-17%

The effect is thus clearly smaller in patients receiving concomitant inducer therapy, more like the effect seen with 4 mg (without inducers). The data broken down by inducer non-inducer use, does more clearly suggest an improved response to 12 mg that do the pooled data, so than we have concluded that dosing should include the 12 mg dose.

Although the data show a fairly marginal effect in patients on inducers, it must be acknowledged that a modest fraction of patients, even if on inducers, do have a substantial (≥ 50%) reduction in seizure rate, so that perampanel has value even in the presence of inducers.

An analysis by Dr. Yang's group sheds light on these outcomes, using seizure rates from studies 304, 305, and 306 and steady state perampanel blood levels from the studies. They divided patients into 4 concentration quartiles (median 55, 132, 209, and 371 mg/ml with inducer and 129, 275, 491, and 876 mg/ml without inducers) and showed median % reduction of seizure frequency for each quartile (see Fig 2). What is clear is that the concentration response relationship is quite similar, whether or not patients are on inducers, but that patients on inducers never reach the concentrations needed for a full effect even with

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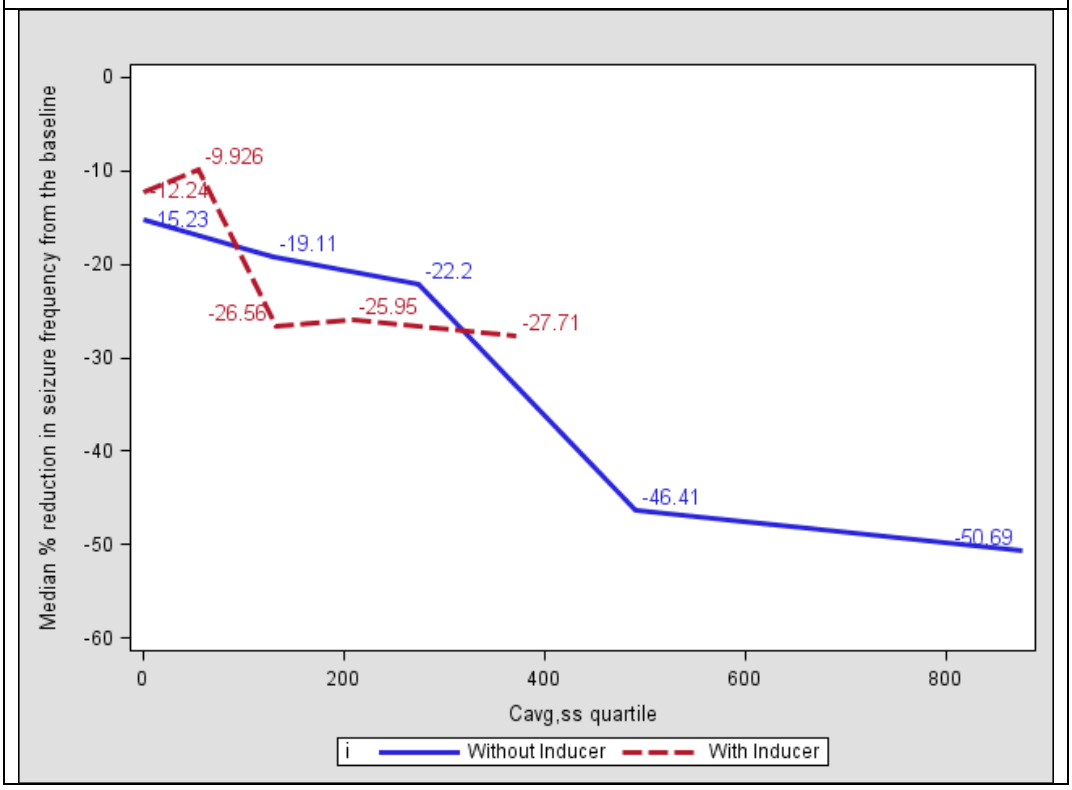
a 12 mg dose. Given the absence of any data on doses above 12 mg, recommending use of higher doses dose not appear appropriate.

Fig 2

Figure 2. Median change in seizure frequency versus steady state average perampanel concentrations in studies of 304/305/306. The effect size is displayed at the median concentrations at each bin.



There seems little doubt that physicians will be tempted to increase the dose of perampanel beyond 12 mg, doses that are essentially unstudied. We are therefore requiring (a post-marketing requirement) a multi-dose safety and effectiveness trial to explore the higher dose-ranges. There is no doubt that this addresses the safety concerns raised by potential use of higher doses than 12 mg, which already has safety concerns sufficient to have led to a Boxed Warning. There is evidence (see below), however, that patients on inducers may be somewhat protected form perampanel's adverse effects.

Results have been examined by demographic subsets, described by Dr. Rusinowitz, and showed no clear relationship to age, gender or race. Examination of data by region showed fairly consistent results in NA, Europe, and Asia-Pacific, but almost no effect in Central and S America, about 15% of the study population. In Central and S American patients had a strikingly large placebo response. It is not likely those regional differences are real.

III. Safety

The safety findings are discussed fully in Dr. Katz's, Dr. Hershkowitz's and Dr. Doi's reviews. A total of over 5,000 patients were studied, about 2,700 in non-seizure related diseases (mostly Parkinson's

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Disease) and 1,600 with epilepsy, 1,038 in RCTs, about 600 of those on perampanel. There was substantial pediatric (12-16) exposure (104), with 82 exposed for > 6 months.

Adverse effects were clearly dose-related, with discontinuation rates because of an adverse effect of 3, 8, and 19% in patients on 4, 8, and 12 mg, vs 5% in placebo. Many patients could not be titrated to their specified dose of 12 mg. Dr. Katz discusses this in depth but, briefly, only about 73% of people achieved their assigned 12 mg dose and only 61% were still on it at the end of treatment. Also of interest, patients on inducing drugs were much more likely to reach their 12 mg target dose. Most common reasons for discontinuing treatment were dizziness, somnolence, vertigo, aggression, anger, ataxia, blurred vision, irritability, and dysarthria.

There is a Boxed Warning concerning the constellation of dose-related psychiatric and behavioral adverse effects, notably hostility and aggression-related effects (irritability, aggression, anger anxiety, belligerence, agitation and physical assault). There were 3 cases of reported homicidal ideation. Perampanel labeling shows the suicidal behavior and ideation concern included in labeling for all AEDs.

Some of the neurologic effects were quite common.

Percent ADRs

	placebo	8 mg	12 mg
Dizziness	9	32	43
Somnolence	7	16	18
Fatigue	5	8	12
Irritability	3	7	12
Fall	3	5	10
Ataxia	0	3	8
Vertigo	1	3	5
Anxiety	1	3	4
Aggression	1	2	3
Anger	< 1	1	3

III. Conclusion

Perampanel is an effective AED for use in people not responding adequately to other therapy. Its average effect is modest, about 15-20% compared to placebo, and is dose-related between 4 and 12 mg, but is reduced by the substantial (> 50% of patients) use of metabolism inducing AEDs, which lower plasma perampanel concentrations by about 50%, yielding a de facto dose of 4 mg in those patients. Higher doses might overcome this, possibly with acceptable toxicity, but, somewhat surprisingly, this has not been studied. Conduct of such a study is a post-marketing requirement.

Perampanel causes a fairly high rate of psychiatric and behavioral problems, notably including aggression/irritability, and also causes dizziness and other neurologic effects, and Somnolence. All of these effects are dose-related. They are described in a Boxed Warning.

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/s/

ROBERT TEMPLE
10/22/2012